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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14,36,38,39 and 41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14, 36, 38-39 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claims 1-4, 6-14, 36, 38-39 and 41-47 are currently pending and under consideration.

Rejections Withdrawn:

All the previous 102 rejections have been withdrawn in view of Applicants amendments to include the limitation that the polydentate chelator is coordinated to a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+} and Ga^{3+}.

All previous 103 rejections have been withdrawn in view of Applicants amendments and arguments therein.

New Rejections and/or Objections:

Claim Objections

Claims 42-45 are objected to because of the following informalities: Claims 42-45 are objected to because they depend from a cancelled claim, and as such, it is unclear what the claims are attempting to further limit. A telephone call was made to Arles Taylor on 1/23/2008 and was conveyed to the Examiner by Chris Perkins that claims 42-45 should be dependent from claim 41. As such, while claims 42-45 are objected for the reasons set forth above, claims 42-45 will be examined as if they are dependent from Claim 41.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 36, 38-39 and 41-47are rejected under 35 U.S.C. 103(a) as being unpatentable over McHahan et al. (Analytical Biochemistry 1996; 236: 101-106, *of record*), or Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*) in view of Wagner et al. (US 7,183,392, 2007), Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116).

McMahan et al. disclose a conjugate comprising polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical to the molecule shown in the instant specification in Figure 7 (see page 103, Figure 1). For example, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, McMahan *et al.* teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan *et al.* teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Lastly, the reference teaches that the conjugate is a unique reagent, which can be used for the detection of histidine-tagged proteins (Title).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a

detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Although Molecular Probes does not specifically teach that the detectable moiety is conjugated to the polydentate chelator at a site other than a potential metal ion coordination site, the claimed limitation does not appear to result in a manipulative difference between the claimed product and that disclosed by the prior art because the specification teaches that biotin-conjugated NTA is commercially available through Molecular probes or can be synthesized following the method of McMahan (described above). Thus, the conjugate appears to be the same as the prior art. Similarly, while Molecular Probes does not specifically teach that the conjugate is soluble in an aqueous medium, the claimed functional limitation would be an inherent property of the referenced product because as evidenced by McMahan *et al.* (*supra*), biotin and nitriloacetic acid conjugates are soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Thus, the claimed "conjugate" appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

As such, both McMahan et al. and Molecular Probes teach a heterobifunctional conjugate comprising a polydentate chelator, a linker and a detectable moiety. However, Neither McMahan et al. nor Molecular Probes explicitly teach that the metal ion is Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} or that the binding solution is in a pH range of 5 to 7.0.

Wagner et al. teach that nitrilotriacetic acid, (NTA), coordinated with metals such as Ni, Co, Fe and Cu bind His-tags of 6 to 9 amino acids column 19, Lines 15-19).

Chaga et al. reviews twenty-five years of immobilized metal ion affinity chromatography (Title). In particular, Chaga et al. teaches that immobilized metal ion affinity chromatography, referred to herein as IMAC, is a separation principle that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein the metal ions can be divided into three

categories (hard, intermediate, and soft) based on their preferential activity towards nucleophiles, wherein hard metals such as Fe3+, Ca2+, Al3+ show preference for oxygen, soft metals such as Cu+, Hg2+, ect. prefer sulfur, and intermediate metals such as Cu2+, Ni2+, Zn2+, Co2+ coordinate to nitrogen, oxygen and sulfur (page 314, 2.Metal ion affinity). For example, the reference teaches that IMAC has seen extensive work in the purification of proteins from complex biological samples such as the use of Cu2+, Ni2+ and Zn2+ for the purification of proteins having exposed Histidine residues, as well as, the use of Fe3+ and Ga3+ for the enrichment of phosphorylated proteins and peptides (page 315, Historical development of IMAC, in particular, last paragraph of page 315, 1st paragraph of 316 and 3rd full paragraph of page 317). The reference further teaches that there are only a few commercially available adsorbents such as IDA and NTA which offer a maximum of tri-(IDA) or tetra (NTA) complexes with the metal ion (page 318, Versatility of the chelating ligands). Lastly, the reference teaches that different absorption selectivity's for a protein within the same sample can be achieved based on whether one uses a hard or intermediate immobilized metal ion. For example, the reference teaches that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu2+ at neutral pH (page 320, Metal ion type).

Zachariou et al. teach the binding properties of immobilised O-phosphoserine (im-OPS) and 8-hydroxyquinoline (im-8-HQ) with immobilised iminodiacetic acid, also referred to as IDA, as the control system in combination with the hard Lewis metal ions, Al3+, Ca2+, Fe3+, Yb3+, and the borderline metal ion, Cu2+, over a pH range of 5.5 to 8.0 (abstract). With regards to the pH, the reference teaches that with a incubation/equilibrium buffer of 0.5 M or 0.06M ionic strength, fewer proteins bound to these hard Lewis metal ion IMAC adsorbents as the pH became increasingly alkaline, which is opposite to what is observed with protein with the borderline Lewis metal ion IMAC systems (page 111, 1st column, last paragraph bridging 2nd column).

Thus, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference to as to modify the heterobifunctional conjugate as taught by McMahan et al. or Molecular probes with Fe3+ in view of the teachings of Wagner et al. One would have been motivated to do so because Wagner et al. teaches that NTA coordinated with Fe3+ binds His-Tags. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the heterobifunctional conjugate

as taught by McMahan et al. or Molecular probes with Fe3+ in view of the teachings of Wagner et al., one would achieve a metal chelate which recognizes a His tag.

Secondly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference so as to substitute the metal ion which coordinates to the heterobifunctional conjugate as taught by McMahan et al. or Moleucular Probes to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by Chaga et al., that different metals such as hard Lewis metals may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Similarly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to use a lower pH binding solution when detecting proteins using hard Lewis metal ions such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by both Chaga and Wagner, that hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Claims 1-2, 4, 6-14 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record), as evidenced by Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737, *of record*), in view of Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a polydentate chelator moiety and a detectable moiety conjugated to the polydentate chelator moiety via a PEG spacer group. With regards to the polydentate chelator moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA). With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further

comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. Etheshami discloses (page 123, Chapter 5) a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA and its application in protein purification and characterization using a two phase system. Moreover, the dissertation teaches the effect of IDA in these biochelates in a two phase system for the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin (page 126). In particular, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. Lastly, the reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20). Thus, while Etheshami does not specifically teach that the conjugate is soluble in an aqueous solution, the claimed functional limitation would be an inherent property of reference conjugate because as evidenced by Ehteshami *et al.* (supra), the presence of the PEG spacer between the chelator-metal ion moiety and the detectable label provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15).

As such, Etheshami teach a heterobifunctional conjugate comprising a polydentate chelator, a linker and a detectable moiety. However, Etheshami et al. does not explicitly teach that the metal ion is Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} or that the binding solution is in a pH range of 5 to 7.0.

Chaga et al. reviews twenty-five years of immobilized metal ion affinity chromatography (Title). In particular, Chaga et al. teaches that immobilized metal ion affinity chromatography, referred to herein as IMAC, is a separation principle that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein the metal ions can be divided into three categories (hard, intermediate, and soft) based on their preferential activity towards nucleophiles, wherein hard metals such as Fe3+, Ca2+, Al3+ show preference for oxygen, soft metals such as Cu+, Hg2+, ect. prefer sulfur, and intermediate metals such as Cu2+, Ni2+, Zn2+, Co2+ coordinate to nitrogen, oxygen and sulfur (page 314, 2.Metal ion affinity). For example, the reference teaches that IMAC has seen extensive work in the purification of proteins from complex biological samples such as the use of Cu2+, Ni2+ and Zn2+ for the purification of proteins having exposed Histidine residues, as well as, the use of Fe3+ and Ga3+ for the enrichment of phosphorylated proteins and peptides (page 315, Historical development of IMAC, in particular, last paragraph of page 315, 1st paragraph of 316 and 3rd full paragraph of page 317). The reference

further teaches that there are only a few commercially available adsorbents such as IDA and NTA which offer a maximum of tri-(IDA) or tetra (NTA) complexes with the metal ion (page 318, Versatility of the chelating ligands). Lastly, the reference teaches that different absorption selectivity's for a protein within the same sample can be achieved based on whether one uses a hard or intermediate immobilized metal ion. For example, the reference teaches that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu2+ at neutral pH (page 320, Metal ion type).

Zachariou et al. teach the binding properties of immobilised O-phosphoserine (im-OPS) and 8-hydroxyquinoline (im-8-HQ) with immobilised iminodiacetic acid, also referred to as IDA, as the control system in combination with the hard Lewis metal ions, Al3+, Ca2+, Fe3+, Yb3+, and the borderline metal ion, Cu2+, over a pH range of 5.5 to 8.0 (abstract). With regards to the pH, the reference teaches that with a incubation/equilibrium buffer of 0.5 M or 0.06M ionic strength, fewer proteins bound to these hard Lewis metal ion IMAC adsorbents as the pH became increasingly alkaline, which is opposite to what is observed with protein with the borderline Lewis metal ion IMAC systems (page 111, 1st column, last paragraph bridging 2nd column).

Thus, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference so as to substitute the metal ion which coordinates to the heterobifunctional conjugate as taught by Etheshami et al to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by Chaga et al., that different metals such as hard Lewis metals may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Similarly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to use a lower the pH of the binding solution when detecting proteins using hard Lewis metal ions such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by both Chaga and Wagner, that hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Claims 36, 37-39 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record), as evidenced by

Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737, *of record*), in view of Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116), as applied to claims 1-2, 4, 6-14 and 41-46 above, and in further view of Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*).

Etheshami in view of Chaga et al. and Zachariou et al. teach, as described above, a heterobifunctional reagent composition comprising a conjugate comprising a polydentate chelator moiety linked to a detectable moiety via a PEG spacer group and a binding solution having a pH of 5.0 to 7.0, wherein the polydentate chelator is coordinated to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+}. The combination further teaches that the conjugates are useful for the purification of proteins such as phosphoroproteins, wherein hard Lewis metals such as Fe3+ and Ga3+ are useful for the enrichment of phosphorylated proteins and peptides

Etheshami in view of Chaga et al. and Zachariou et al. does not explicitly teach a kit comprising the components as described above.

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit.

Thus, it would have been prima facie obvious to one of skill in the art at the time the invention was made to package the chelated metal conjugate as taught by Etheshami in view of Chaga et al. and Zachariou et al. into a kit useful for the detection of a polypeptide fragments in view of the teachings of Molecular Probes because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time the invention was made would have been motivated to make a kit useful for the detection of polypeptides because standard kits enhance the

probability of reproducibility and efficiency of the detection process, and further, provide for increased marketability, convenience, reliability and economy.

(Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous use of the Etheshami et al dissertation in the prior 103 rejection (Remarks beginning on page 14, III.B).

With regards to the Etheshami et al. dissertion, Applicants assert that the Patent Office's reference to page 126 of Ehtheshami does not support the instant rejection. For example, Applicants assert that the page 126 of Ehtheshami discloses the following:

> the specificity of the bioligand moiety of these biopolymers (biotin, and PAB) were tested by adding them to two-phase systems, without charging the chelate side with metal ions. Similarly, and in order to characterize the pseudo-affinity chelating effect, experiments were performed by charging it with metal ions first and then added to the two-phase systems, containing the protein, hemoglobin, rich in surface histidine (20 histidines) which has affinity for chelated metal-ions, but having no affinity for PAB or biotin. (Emphasis added)

Thus, Applicants assert that this passage clearly indicates that the charged chelates were employed for testing for pseudo-affinity chelating, which refers to background, non-specific partitioning that results not from a desirable interaction of a target with a bioligand (i.e., biotin or PAB), but from an undesirable, non-specific interaction of the metal ion with, for example, surface histidines. Therefore, Applicants contend that the experiments described on page 126 of Ehteshami are experiments to assess the background, non-specific binding that is attributable not to the desired interaction between the bioligand and its binding partner, but to the interaction of the surface histidines on non-target proteins with the metal ion. Applicants further submit that this is clear from the juxtaposition of the two conditions presented on page 126 that the investigator whished to determine to what extent the non-specific interaction would occur. As such, Applicants contend that the disclosure of Ehteshami cannot be read to suggest that there is a desirable, specific interaction between the chelated metal ion and the target protein, which is in marked contrast to the nature of the presently claimed reagents which desire specific interaction between the target proteins and the chelated metal. In fact, Applicants respectfully submit that page 132 of Ehteshami explicitly

states that "as it can be seen from Table 2.1-2, the presence of the metal ions in bioligands-PEG-IDA-Cu(II) has no significant effect on the partitioning of avidin (emphasis added).

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges Applicants conclusions pertaining to the Ehteshami dissertation and does not dispute Applicants quotation of the specific passages presented on pages 126. However, the Examiner recognizes that Ehteshami does not appear to teach or suggest that the experiments for testing pseudoaffinity, refers to the "background, non-specific partitioning," nor does it teach or suggest that these "results" are undesirable as asserted by Applicants. In contrast, the Examiner recognizes that Ehteshami on page 126 clearly teaches that "[T]he dual affinity of these modified PEG's enhanced the partitioning of the model proteins as compared to these modified PEG derivatives incorporated into the same two-phase systems." (emphasis added) Regarding Applicants assertions pertaining to the passage on page 132, the Examiner acknowledges and does not dispute that on page 132 Ehteshami explicitly states that "as it can be seen from Table 2.1-2, the presence of the metal ions in bioligands-PEG-IDA-Cu(II) has no significant effect on the partitioning of avidin. However, the Examiner recognizes that Ehteshami et al. explains this result and attributes it to "saturation" of all of the binding sites of the protein with biotin. For example, the sentence prior to the passage quoted by Applicants recites "[S]ince enough biotin-PEG-IDA or biotin-PEG-IDA/Cu(II) was initially added to the two phase systems, all of the binding sites on the protein might have been occupied by biotin and no sites were left for metal ion's interactions." As such, it appears that Applicants have misinterpreted these experimental results. Lastly, as stated above, the Examiner recognizes that Ehteshami disclose (page 83 and 89) a heterobifunctional conjugate comprising a polydentate chelator moiety linked to a detectable moiety via a PEG spacer group. In other words, Ehteshami teaches a heterobifunctional detection reagent which appears to be identical to that which is claimed with the exception of the metal and pH. However, in view of the teachings of Chaga et al. and Zachariou et al., those of skill in the art recognize that different metals such as hard Lewis metals Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}; and further, hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Thus, the combination of the taught heterobifunctional agent, known hard Lewis metal, and a lower pH binding solution provides no more than predictable results.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF